Systemic fungal infection
Candidiasis
Antifungal drugs

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Systemic fungal infections

- **Fungal infections, or mycoses, depending on the degree of tissue invasion are classified as:-**
  - **Superficial.**
  - **Subcutaneous.**
  - **Systemic (deep),.**
- **Fungal infections have an increasingly important role as use of broad-spectrum antimicrobial agents has increased and the number of immunodeficient patients has grown.**

Systemic fungal infections

- **Some pathogens (e.g., Cryptococcus, Candida, Pneumocystis, Fusarium) rarely cause serious disease in normal hosts.**

- **Other endemic fungi (egg, Histoplasma, Coccidioides, Paracoccidioides)**
  - **Commonly cause disease in normal hosts.**
  - **More aggressive in immunocompromised ones.**

Systemic fungal infections

❑ Aspergillosis :-

- ➢ An opportunistic systemic mycosis, which affects the respiratory tract predominantly.

- ➢ Aspergillus fumigatus is the usual cause of aspergillosis.

Systemic fungal infections

- **Aspergillosis :-**

❖ **Clinical Findings :-**

A. Allergic Bronchopulmonary Aspergillosis

- **In patients with preexisting asthma.**
  - **Develop worsening bronchospasm.**
  - **Fleeting pulmonary infiltrates.**
  - **Accompanied by eosinophilia, high levels of IgE, and IgG Aspergillus precipitins in the blood.**
- **May complicate cystic fibrosis.**

Systemic fungal infections

- **Aspergillosis :-**

❖ Clinical Findings :-

B. Invasive Aspergillosis

- Invasive manifestations may be seen in immunocompetent or only mildly immunocompromised adults.
- These include the following :-

1. Sinusitis :-

- Sinus involvement is usually diagnosed histologically after patients with chronic sinus disease undergo surgery.

2. Aspergillomas :-

- Aspergillomas of the lung occur when preexisting lung cavities become secondarily colonized with Aspergillus species.
- May be found by incidental radiographic studies, may present with significant hemoptysis.

Systemic fungal infections

- **Aspergillosis :-**

❖ Clinical Findings :-

3. Chronic necrotizing aspergillosis :-

- **Invasive manifestation is a relatively rare disease seen in patients with some degree of immunocompromise and presents with a protracted course compared with the more common acute invasive form of the disease.**

- **Fibrosis and cavity formation may be prominent.**

Systemic fungal infections

- **Aspergillosis :-**

❖ Clinical Findings :-

4. Life-threatening invasive aspergillosis

➢ **Most commonly occurs in profoundly immunodeficient patients, particularly in patients:-**

- **Have undergone hematopoietic stem cell transplants.**
- **In those with prolonged, severe neutropenia.**
- **In patients with chronic granulomatous disease.**

Systemic fungal infections

❑ Aspergillosis :-

❖ Clinical Findings :-

4. Life-threatening invasive aspergillosis

➢ **Specific risk factors in patients who have undergone a hematopoietic stem cell transplant include:-**

- **Cytopenia's.**
- **Corticosteroid use.**
- **Iron overload.**
- **Cytomegalovirus disease.**
- **Graft-versus-host disease.**

Systemic fungal infections

- **Aspergillosis :-**

❖ Clinical Findings :-

4. Life-threatening invasive aspergillosis

- **Acute IPA causes a severe necrotizing pneumonia and must be considered in any immunocompromised patient who develops:-**

- **Fever.**
- **New respiratory symptoms (particularly pleural pain or hemoptysis).**
- **A pleural rub.**

Systemic fungal infections

- **Aspergillosis :-**

❖ Clinical Findings :-

4. Life-threatening invasive aspergillosis

- **Invasion of pulmonary vessels causes thrombosis and infarction.**
- **Invasive sinus disease also occurs.**
- **May be hematogenous dissemination to the central nervous system, skin, and other organs.**
- **Early diagnosis and reversal of any correctable immunosuppression are essential.**

Systemic fungal infections

❑ Aspergillosis :-

❖ Investigations :-

- Blood cultures have very low yield.
- ELISA or PCR, or both, has been used for the early diagnosis of invasive disease.
- ELISA and PCR can be tested in serum or in bronchoalveolar lavage fluid, which may be more sensitive compared to serum.
- A definitive diagnosis requires demonstration of Aspergillus in tissue or culture from a sterile site.
- CT scan of the chest may show characteristics suggestive of invasive aspergillosis (e.g., “halo sign”).

Systemic fungal infections

- **Aspergillosis :-**

❖ Prevention :-

➢In areas with high spore counts, patients are advised to wear a mask if venturing outside their hospital room.

➢Posaconazole or itraconazole may be prescribed for primary prophylaxis.

➢Patients with a history of definite or probable IPA should be considered for secondary prophylaxis before further immunosuppression.

➢ Widespread use of broad-spectrum azoles raises concern for development of invasive disease by highly resistant fungi.

Systemic fungal infections

- **Aspergillosis :-**

❖ Treatment :- Life-threatening invasive aspergillosis; :-

- **The mortality rate of pulmonary or disseminated disease in the immunocompromised patient remains well above 50%, particularly in patients with refractory neutropenia, and if treatment is delayed.**

- **When severe invasive aspergillosis is considered clinically likely or is demonstrable by laboratory testing, rapid institution of voriconazole (i.v) is considered optimal therapy.**

- **Alternatives include a lipid formulation of amphotericin B, Caspofungin intravenously, and Posaconazole oral tablets.**

- **Addition of Caspofungin to liposomal amphotericin B or voriconazole therapy in critically ill patients who are not responding to conventional antifungal treatment.**

Systemic fungal infections

❑ Aspergillosis :-

❖ Treatment :- Life-threatening invasive aspergillosis; :-

- Oral dosing of voriconazole can be used for less serious infections or as a step-down strategy after intravenous therapy.

- Response may be assessed clinically, radiologically and serologically (by estimation of the circulating galactomannan level).

- Surgical debridement is generally done for:-
  - Sinusitis.
  - Focal pulmonary lesions, especially for treatment of life-threatening hemoptysis.

Systemic fungal infections

- **Aspergillosis :-**

❖ **Treatment :- Life-threatening invasive aspergillosis; :-**

➢**Patients at risk of Aspergillus (and other fungal infections) should be managed in rooms with high-efficiency particulate air (HEPA) filters and laminar airflow.**

➢**Therapeutic drug monitoring should be considered for both voriconazole and Posaconazole given variations in metabolism and absorption.**

Systemic fungal infections

Cryptococcosis :-

- Cryptococcosis is a systemic mycosis caused by two environmental yeast species, Cr. neoformans and Cr. gattii.

- Cr. Neoformans is distributed worldwide and is primarily an opportunistic pathogen, most commonly associated with HIV infection.

- Cryptococcosis is acquired by inhalation of yeasts.

- May disseminate to any organ, most commonly the CNS and skin.

- Cr. neoformans are most severe in immunocompromised individuals.

- Cr. gattii causes severe disease in immunocompetent hosts.

- Disseminated cryptococcosis is largely restricted to immunocompromised patients.

Systemic fungal infections

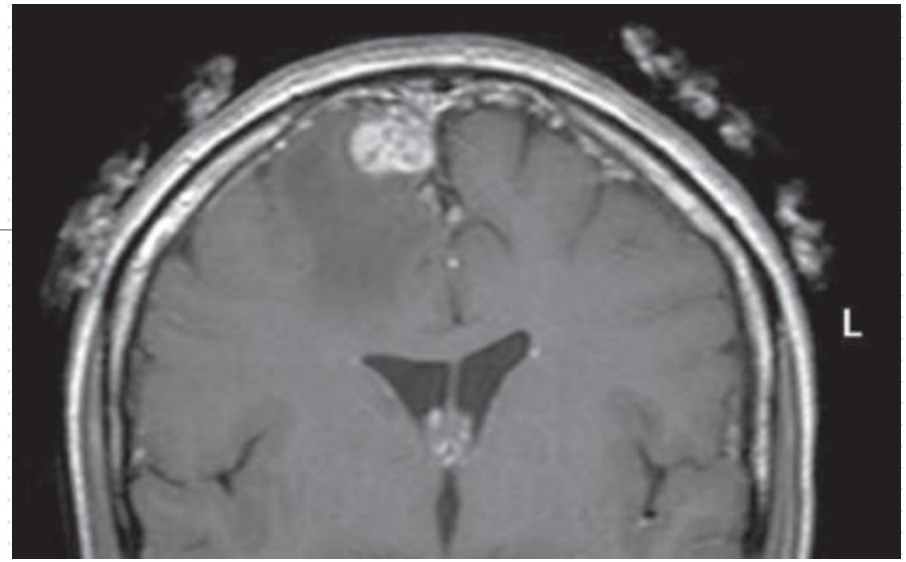
❑ Cryptococcosis :-

❖ Clinical features

- CNS manifestations of cryptococcosis include meningitis and cryptococcoma.
- Pulmonary cryptococcosis manifestations of range from severe pneumonia to asymptomatic disease with single or multiple pulmonary nodules, sometimes cavitation.
- Cryptococcal nodules may mimic other causes of lung pathology, such as TB or malignancy.

Systemic fungal infections

❑ Cryptococcosis :-



❖ Diagnosis:-

➢Requires histopathology and/or culture.

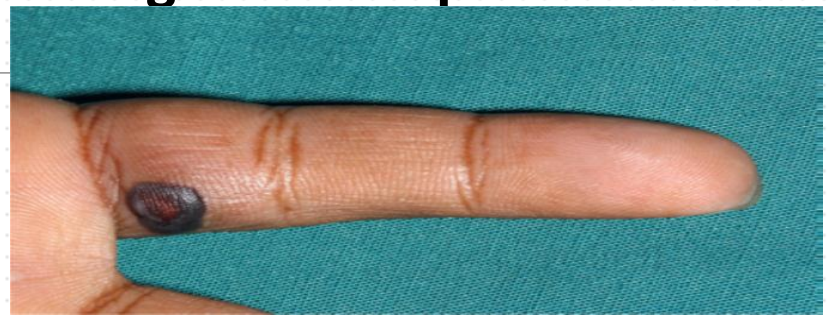
❖ Treatment:-

- ➢ Treatment of severe cryptococcosis is the same as for cryptococcal meningitis, initially with liposomal amphotericin B.
- ➢ Mild pulmonary disease is usually treated with fluconazole.
- ➢ A symptomatic nodules resection of the lesions is likely to be sufficient.

Systemic fungal infections

❑ Fusariosis :-

- Fusarium spp. cause disseminated disease in patients with prolonged neutropenia.



- The disease presents with antibiotic-resistant.
- Manifestations by fever and evidence of dissemination (e.g. skin nodules, endophthalmitis, septic arthritis, pulmonary disease.
- Fusarium spp. Is often recovered from blood cultures.
- Treatment agents; voriconazole, Posaconazole or lipid-formulated amphotericin B is most often prescribed.

Systemic fungal infections

❑ Mucormycosis :-

- Mucormycosis is a severe but uncommon opportunistic systemic mycosis caused by a number of ‘micaceous’ moulid’s.

- Disease patterns include rhino cerebral/craniofacial, pulmonary, cutaneous and systemic disease.

- Characterized by the rapid development of severe tissue necrosis, which is almost always fatal if left untreated.

- The most common predisposing factors are profound immunosuppression from:-
  - Neutropenia and/or hematopoietic stem cell transplantation.
  - Uncontrolled diabetes mellitus.

  - Iron chelation therapy with deferoxamine.
  - Severe burns.

Systemic fungal infections

❑ Mucormycosis :-

➢ Definitive diagnosis:-

- Culture but histopathological confirmation is required.

➢ Treatment:-

- Requires a combination of antifungal therapy and surgical debridement, with correction of predisposing factor(s) if possible.

➢ High-dose lipid-formulated amphotericin B is most commonly used.

➢ Posaconazole may be used as a second-line agent or as oral ‘step-down’ therapy.

Systemic fungal infections

❑ Talaromyces (formerly Penicillium) marneffei infection :-

- T. marneffei is a thermally dimorphic pathogen.
- Mainly in association with HIV infection .

- Acquisition is usually by inhalation of environmental spores, with primary lung infection followed by hematogenous dissemination.

- A generalized popular rash, which progresses to widespread necrosis and ulceration, is a characteristic feature.
- Skin lesions may resemble molluscum contagiosum.

- Diagnosis is by histopathology and/or culture of respiratory secretions, blood or any infected clinical material.

- Treatment involves an amphotericin B formulation followed by itraconazole (in severe infection), or itraconazole alone.

Systemic fungal infections

Histoplasmosis :-

- A primary systemic mycosis caused by the dimorphic fungus Histoplasma capsulatum.
- The primary reservoir of H. capsulatum is soil enriched by bird and bat droppings, in which the fungus remains viable for many years.
- Infection is by inhalation of infected dust.
- Natural infections are found in bats, which represent a secondary reservoir of infection.
- Histoplasmosis is a specific hazard for explorers of caves and people who clear out bird roosts.

Systemic fungal infections

❑ Histoplasmosis :-

- The organism is inhaled in the form of conidia or hyphal fragments and transforms to the yeast phase during infection.
- Conidia or yeasts are phagocytosed by alveolar macrophages and neutrophils, and this may be followed by hematogenous dissemination to any organ.
- Subsequent development of a T-lymphocyte response brings the infection under control, resulting in a latent state in most exposed individuals.

Systemic fungal infections

❑ Histoplasmosis :-

❖ Clinical features :-

- Disease severity depends on the quantity of spores inhaled and the immune status of the host.
- In most cases, infection is asymptomatic.
- Pulmonary symptoms are the most common presentation, with fever, non-productive cough and an influenzalike illness.
- Erythema nodosum, myalgia and joint pain frequently occur.
- Chest radiography may reveal a pneumonitis with hilar or mediastinal lymphadenopathy.
- Other disease patterns include a visceral form with liver and splenic invasion, and disseminated disease.

Systemic fungal infections

❑ Histoplasmosis :-

❖ Clinical features :-

- May develop chronic pulmonary histoplasmosis (CPH) in patients with (COPD) or emphysema .
- The predominant features of this condition, which may easily be mistaken for tuberculosis.
-
- Radiological findings include fibrosis, nodules, cavitation and hilar/mediastinal lymphadenopathy.

Systemic fungal infections

❑ Histoplasmosis :-

❖ Clinical features :-

- disseminated disease.

❑ Acute disseminated histoplasmosis

- Is seen with immunocompromise.

- Features include fever, pancytopenia, hepatosplenomegaly, lymphadenopathy and often a papular skin eruption.

❑ Chronic disseminated disease presents with;

- Fever, anorexia and weight loss.

- Cutaneous and mucosal lesions, lymphadenopathy, hepatosplenomegaly and meningitis.

Systemic fungal infections

❑ Histoplasmosis :-

❖ Investigations :-

- ➢ **Histoplasmosis should be suspected in endemic areas with every undiagnosed infection in which there are:-**
  - **Pulmonary signs.**
  - **Enlarged lymph nodes.**
  - **Hepatosplenomegaly.**
  - **Characteristic cutaneous/bony lesions.**

- ➢ **Radiological**
  - ✓ **In long-standing cases may show calcified lesions in the lungs, spleen or other organs.**
  - ✓ **In acute phases of the disease, single or multiple soft pulmonary shadows with enlarged tracheobronchial nodes.**

Systemic fungal infections

❑ Histoplasmosis :-

❖ Investigations :-

➢ Laboratory diagnosis

- ✓ By direct detection (histopathology or antigen detection), culture and serology.
- ✓ Antigen detection is the most effective method, it is not widely available.
- ✓ Culture is definitive but slow (up to 12 weeks).
- ✓ Diagnosis of subcutaneous or bony infection is mainly by histopathological examination and/or culture.

Systemic fungal infections

❑ Histoplasmosis :-

❖ Management :-

➢ Mild pulmonary disease:-

- Not require treatment.
- Treated with itraconazole, if prolonged.

➢ Severe pulmonary disease:-

- Treated with an amphotericin B formulation, followed by itraconazole.
- Methylprednisolone added for the first 2 weeks of therapy if there is hypoxia or ARDS.

➢ CPH is treated with itraconazole oral solution for 12–24 months.

Systemic fungal infections

❑ Histoplasmosis :-

❖ Management :-

➢ Disseminated histoplasmosis:-

- Treated with an amphotericin B formulation followed by itraconazole.

- Lipid formulations of amphotericin B are preferred but their use is subject to availability.

➢ In subcutaneous and bone infection, patterns of remission and relapse are more common than cure.

➢ A solitary bony lesion may require local surgical treatment only.

Systemic fungal infections

❑ Coccidioidomycosis :-

- A primary systemic mycosis caused by the dimorphic fungi Coccidioides immitis and C. posadasii.
- The disease is acquired by inhalation of conidia (arthrospores).
- In 60% of cases it is asymptomatic but in the remainder it affects the lungs, lymph nodes and skin.
- Rarely, it may spread hematogenous to other organs, particularly in those with immunocompromise.
- Pulmonary coccidioidomycosis has two forms: primary and progressive.

Systemic fungal infections

❑ Coccidioidomycosis :-

- In symptomatic, primary coccidioidomycosis presents with cough, fever, chest pain, dyspnea and (commonly) arthritis and a rash (erythema multiforme).
- Progressive disease presents with systemic upset (e.g. fever, weight loss, anorexia) and features of lobar pneumonia, and may resemble tuberculosis.
- Coccidioides meningitis is the most severe disease manifestation; it is fatal if untreated and requires life-long suppressive therapy with antifungal azoles.

Systemic fungal infections

❑ Coccidioidomycosis :-

❖ Investigations

- Diagnosis is by direct histopathological detection in specimens, culture of infected tissue or fluids, or antibody detection.
- IgM may be detected after 1–3 weeks of disease by precipitin tests. IgG appears later.
- Change in IgG titer may be used to monitor clinical progress.

Systemic fungal infections

❑ Coccidioidomycosis :-

❖ Management

- Treatment depends on specific disease manifestations.
- Regular clinical reassessment without antifungal therapy (in mild pulmonary, asymptomatic cavitary or single nodular disease).
- High-dose treatment with an antifungal azole, which may be continued indefinitely (e.g. in meningitis).
- Amphotericin B is used in diffuse pneumonia, disseminated disease and, intrathecally, in meningitis.
- Posaconazole has been used successfully in refractory disease.

Systemic fungal infections

❑ Paracoccidioidomycosis :-

- A primary systemic mycosis caused by inhalation of the dimorphic fungus Paracoccidioides Brasiliense's, which is restricted to South America.

- The disease affects the lungs, mucous membranes, skin, lymph nodes and adrenal glands (hypoadrenalism).

- Diagnosis is by microscopy and culture of lesions, and antibody detection.

- Oral itraconazole solution (200 mg/day) is currently the treatment of choice.

- Ketoconazole, fluconazole, voriconazole and 2–3-year courses of Sulphonamides are alternatives.

- Amphotericin B is used in severe or refractory disease, followed by an azole or Sulphonamides.

Systemic fungal infections

❑ Blastomycosis :-

- Blastomyces dermatitidis is a dimorphic fungus.

- Usually presents as a chronic pneumonia similar to pulmonary tuberculosis.
- Bones, skin and the genitourinary tract may also be affected.
- Diagnosis is by culture of the organism or identification of the characteristic yeast form in a clinical specimen.
- Antibody detection is rarely helpful.
- Treatment is with amphotericin B (severe disease) or itraconazole

Candidiasis

❖ Superficial candidiasis :-

- Caused by Candida spp., mainly C. albicans.
- Manifestations include oropharyngeal and vaginal candidiasis (‘thrush’), intertrigo and chronic paronychia.
- Superficial candidiasis often follows antibiotic therapy.
- Superficial candidiasis is treated mainly with topical azoles, oral azoles being reserved for refractory or recurrent disease.
- Severe oropharyngeal and esophageal candidiasis is a consequence of CD4+ T-lymphocyte depletion/ dysfunction, as in HIV infection.
- Recurrent vaginal or penile candidiasis may be a manifestation of diabetes mellitus.

Candidiasis

❖ Systemic candidiasis :-

➢ **Is an opportunistic mycosis caused by Candida spp.**

➢ **Candidiasis is:-**

✓ **Usually an endogenous disease that originates from colonization in;-**

- **Oropharyngeal.**
- **Genitourinary.**
- **Skin.**

✓ **Nosocomial spread can be occurs.**

Candidiasis

❖ **Systemic candidiasis :- Syndromes of systemic candidiasis**

❑ **Acute disseminated candidiasis**

- **The main predisposing factor is the presence of a central venous catheter.**
- **Other major factors include recent abdominal surgery, a disease of intensive care, total parenteral nutrition (TPN), recent antimicrobial therapy and localized Candida colonization.**
- **Up to 40% of cases will have ophthalmic involvement, with characteristic retinal 'cotton wool' exudates.**
- **Skin lesions (non-tender pink/ red nodules) may be seen.**
- **Renal tract candidiasis, osteomyelitis, septic arthritis, peritonitis, meningitis and endocarditis are all well recognized and are usually sequelae of acute disseminated disease.**

Candidiasis

❖ **Systemic candidiasis :-**

❑ **Chronic disseminated candidiasis (hepatosplenic candidiasis)**

➢ **Suggests a diagnosis of hepatosplenic candidiasis if Persistent fever in a neutropenic patient, despite antibacterial therapy and neutrophil recovery.**

➢ **Associated with :-**

✓ **Development of abdominal pain.**

✓ **Raised alkaline phosphatase.**

✓ **Multiple lesions in abdominal organs (e.g. liver, spleen and/or kidneys) on radiological imaging.**

➢ **This represents a form of immune reconstitution syndrome in patients recovering from neutropenia and usually lasts for several months, despite appropriate therapy.**

Candidiasis

❖ **Systemic candidiasis :-**

❖ **Management :-**

➢ **Blood cultures positive for Candida spp. must never be ignored.**

❑ **Acute disseminated candidiasis**

❖ **Treated with antifungal therapy.**

❖ **Removal of any in-dwelling central venous catheter (whether known to be the source of infection or not).**

❖ **Removal of any documented source.**

➢ **Candidemia should be treated initially with an echinocandin, with subsequent adjustment (usually to intravenous or oral fluconazole) guided by clinical response, species identification and susceptibility testing.**

➢ **Treatment should continue for a minimum of 14 days.**

➢ **Alternative therapies include voriconazole and amphotericin B formulations.**

Candidiasis

❖ **Systemic candidiasis :-**

❖ **Management :-**

❑ **Chronic disseminated candidiasis**

❖ **Requires prolonged treatment over several months with fluconazole or other agents, depending on species and clinical response.**

❖ **The duration may be reduced by adjuvant therapy with systemic glucocorticoids.**

❖ **Diagnosis and treatment of these conditions require specialist mycological advice.**

Antifungal agents

❖ Azole antifungals :-

- The azoles (imidazole's and triazoles) inhibit synthesis of ergosterol, a constituent of the fungal cell membrane.

- Side-effects include gastrointestinal upset, hepatitis and rash.

- Azoles are inhibitors of cytochrome P450 enzymes, so tend to increase exposure to cytochrome P450-metabolised drugs.

❑ Imidazole’s :-

- Miconazole, econazole, clotrimazole and ketoconazole are relatively toxic and therefore administered topically.

- Clotrimazole is used extensively to treat superficial fungal infections.

Antifungal agents

❖ Azole antifungals :-

❑ Triazoles :-

- Used for systemic treatment because they are less toxic.
- Triazoles Fluconazole is effective against yeasts (Candida and Cryptococcus spp.) and has a long half-life (approximately 30 hours) and an excellent safety profile.
- The drug is highly water-soluble and distributes widely to all body sites, including CSF.

❑ Itraconazole

- Is lipophilic and distributes extensively, including to fingernails.
- Poor CSF penetration.

Antifungal agents

❖ Azole antifungals :-

❑ Voriconazole

- ➢ Well absorbed orally but variability in levels requires therapeutic drug monitoring.
- ➢ Used mainly in aspergillosis.
- ➢ Side-effects include photosensitivity, hepatitis and transient retinal toxicity.

❑ Posaconazole and isavuconazole

- ➢ Are broad-spectrum azoles.
- ➢ Active against Candida spp., Aspergillus spp. and some micaceous moulid's.

❑ Isavuconazole

- ➢ Is non-inferior to voriconazole in the management of invasive aspergillosis.
- ➢ May be considered as an alternative when voriconazole is not tolerated.

Antifungal agents

❖ Echinocandins :-

- The echinocandins inhibit β-1,3-glucan synthesis in the fungal cell wall.
- Have few significant adverse effects.
- Caspofungin, anidulafungin and micafungin are used to treat systemic candidiasis.
- Caspofungin is also used in aspergillosis.

Antifungal agents

❖ Polyenes :-

❑ Amphotericin B (AmB) deoxycholate

- Causes cell death by binding to ergosterol and damaging the fungal cytoplasmic membrane.

- Its largely supplanted by less toxic agents.
- Its long half-life enables once-daily administration.
- Poor CSF penetration.
- Adverse effects include immediate anaphylaxis, other infusion related reactions and nephrotoxicity.
- Nephrotoxicity may be sufficient to require dialysis and occurs in most patients who are adequately dosed.
- Irreversible nephrotoxicity occurs with large cumulative doses of AmB.

Antifungal agents

❖ Polyenes :-

❑ Lipid formulations of AmB :-

- Developed to reduce AmB toxicity and have replaced AmB deoxycholate in many regions.

- Adverse effects are similar to, but less frequent than, those with AmB deoxycholate, and efficacy Is similar.

- Used in invasive fungal disease, as empirical therapy in patients with neutropenic fever, and in visceral leishmaniasis

❑ Nystatin :-

- A similar spectrum of antifungal activity to AmB.

- Toxicity limits it to topical use, e.g. in oral and vaginal candidiasis.

Antifungal agents

❖ Other antifungal agents :-

❑ Flucytosine

- Flucytosine (5-fluorocytosine) has particular activity against yeasts.
- Should be given in combination with another antifungal agent to prevent resistance.
- Adverse effects include myelosuppression, gastrointestinal upset and hepatitis.

❑ Griseofulvin

- Griseofulvin has been largely superseded by terbinafine and itraconazole for treatment of dermatophyte infections, except in children.

Antifungal agents

❖ Other antifungal agents :-

❑ Terbinafine

- Distributes with high concentration to sebum and skin, with a half-life of more than 1 week.
- Used topically for dermatophyte skin infections and orally for onychomycosis.
- The major adverse reaction is hepatic toxicity.
- Terbinafine is not recommended for breastfeeding mothers.

Thank you